METHOD AND APPARATUS FOR STIMULATING ANGIOGENESIS AND WOUND HEALING BY USE OF EXTERNAL COMPRESSION

Background of the Invention

External compression techniques including enhanced external counterpulsation (EECP) have been used for many years to increase circulation and provide support for a failing heart. EECP generally involves placing inflatable cuffs on the low half of a patient's body and pressurizing and depressurizing the cuffs out-of-phase with the left ventricle. Pressurization of the cuffs during diastole when the aortic valve is closed leads to collapse of the arteries causing blood to flow retrograde from the extremities to the heart. The resulting increased diastolic pressure has been shown to increase perfusion of vital organs including the heart. Measurements performed by Applebaum *et al.* have demonstrated increases in mean flow velocities of 19% and 22% in the renal and carotid arteries, respectively (Applebaum *et al.* "Sequential external counterpulsation increases cerebral and renal blood flow" *American Heart Journal* 133(6):611-615, June 1997; incorporated herein by reference). Just prior to systole, the cuffs are depressurized to allow the arteries to refill. Depressurization of the cuff at this time is thought to lead to a rarefaction wave which propagates back to the heart resulting in a decrease in cardiac afterload. As in the case of coronary perfusion enhancement, the benefits of afterload reduction are relatively small, and EECP has not found general acceptance as a cardiac assist procedure.

One of the best ways of alleviating the problems of low blood flow and decreased perfusion is through angiogenesis in order to create new blood vessels to feed the affected area of the body. Angiogenesis has been found to be important in many pathological conditions such as cancer and retinal neovascularization as well as in normal physiological states such as wound

healing and development. Angiogenesis is a complex biological process involving many factors and cell types to produce new blood vessels. Many natural factors have been found to have angiogenic activity including platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, *etc.* Arterial and venous endothelial cells and smooth muscle cells have been found to be sensitive to fluid dynamic shear stress and mechanical strain and to release pro-angiogenic factors (*e.g.*, platelet-derived growth factors A and B, and basic fibroblast growth factor) in response to such stimuli (Davies "Mechanisms involved in endothelial responses to hemodynamic forces" *Atherosclerosis* 131:S15-S17, June 1997; Diamond *et al.* "Tissue plasminogen activator messenger RNA levels increase in cultured human endothelial cells exposed to laminar shear stress" *Journal of Cell Physiology* 143:364-371, 1990; Hseih *et al.* "Shear stress increases endothelial platelet-derived growth factor mRNA levels" *American Journal of Physiology* 260:H642-H646, 1991; Malek *et al.* "Fluid shear stress differentially modulates expression of genes encoding basic fibroblast growth factor and platelet-derived growth factor B chain in vascular endothelium" *Journal of Clinical Investigation* 92:2013-2021, 1993; Mason "The ins and outs of fibroblast growth factors" *Cell* 78(4):547-552, August 1994; Mitsumata *et al.* "Fluid shear stress stimulates platelet-derived growth factor expression in endothelial cells" *American Journal of Physiology* 265(1):H3-H8, July 1993; Sumpio "Hemodynamic forces and the biology of the endothelium: signal transduction pathways in endothelial cells subjected to physical forces in vitro" *Journal of Vascular Surgery* 13(5):744-746, May 1991; Ichioka *et al.* "Effects of shear stress on wound-healing angiogenesis in the rabbit ear chamber" *Journal of Surgical Research* 72:29-35, 1997; each of which is incorporated herein by reference). Shear stress is also instrumental in the control

of nitric oxide, endothelin-1, transforming growth factor•$_1$, and a host of others, many of which may also contribute to angiogenesis.

Although in pathological conditions such as cancer one would like to inhibit the growth of new blood vessels to prevent the growth and spread of cancerous cells, many patients with vascular disease such as coronary artery disease, peripheral vascular disease, diabetes, and atherosclerosis would benefit from the formation of new blood vessels. These new blood vessels would provide better perfusion of the affected area and would lead to the alleviation of symptoms including claudication, numbness, coldness, loss of sensation, and pallor. Currently patients with mild to moderate peripheral vascular disease are advised to exercise the affected area to increase blood flow, and vascular operations to replace diseased vessels with grafts are reserved for more severe cases.

There remains a need for a system of inducing angiogenesis in patients with wounds or vascular disease via a non-invasive method. This system would provide a more pro-active approach to patients with mild to moderate disease and allow for the treatment of a patient with more severe disease without the risks of operations.

Summary of the Invention

The present invention provides a system for inducing angiogenesis through endogenous pathways by stimulating endothelial cells, smooth muscle cells, or other cells to produce angiogenic factors. Endothelial cells are known to respond to changes in their environment such as shear stress, mechanical strain, and other hemodynamic forces and produce various angiogenic factors. By altering the shear stress or other hemodynamic forces experienced by the

endothelial cells or smooth muscle cells using external compression, one may induce these cells to produce the desired factors and thereby induce angiogenesis.

Any form of external compression may be used which leads to a change in the shear stress or other hemodynamic forces sensed by the endothelial cells, smooth muscle cells, or other cells and leading to the production of angiogenic factors. The maximum pressure needed to attain such a change in the shear stress is typically below that normally used in EECP and other cardiac assist devices. The compression may be applied to the body in a graded and/or sequential manner.

In one aspect, the present invention provides a method of treating a disease characterized by low blood flow (*e.g.*, peripheral vascular disease, coronary artery disease, atherosclerosis, *etc.*) by inducing angiogenesis. A patient suffering from a disease characterized by low blood flow is provided, and a compression apparatus which can provide external compression is attached to the patient's body. The apparatus is used to compress at least one part of the pateint's body in a manner sufficient to induce angiogenesis. Without wishing to be bound by a particular theory, the external compression is thought to induce angiogenesis by altering the shear stress or other mechanical force experienced by the cells of the patient's vasculature. This change in shear stress leads to the production of various angiogenic factors by the endothelial cells, and these factors subsequently act on various cells to induce the growth of new blood vessels.

The pressure applied to the patient using external compression is typically less than 300 mm Hg. The resulting change in shear stress in certain preferred embodiments is a change in the sign of the stress indicating a change in the direction of the flow of blood in the vessels. In another preferred embodiment, the shear stress is changed in the vessels by 50%, more

preferably 100%, more preferably 200%, and most preferably 400%. In another preferred embodiment, the compression applied to the body part is graded (*i.e.*, the maximum level of pressure applied is greatest in the periphery and falls off in the direction of the heart) and/or sequential (*i.e.*, the pressure wave starts peripherally and proceeds proximally).

In a preferred embodiment, the angiogenic factors produced by the vascular cells in response to the external compression include, but are not limited to, growth factors (*e.g.*, platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, transforming growth factor• $_1$, *etc.*), cytokines, prostaglandins, leukotrienes, endothelin-1, and nitric oxide (NO). In a preferred embodiment, the cells responding to the change in hemodynamic factors and responsible for producing the angiogenic factors may be endothelial cells, muscle cells, fibroblasts, epithelial cells, or smooth muscle cells.

In another preferred embodiment, the patient being treated using the inventive method suffers from a wound and would benefit from enhanced wound healing. The wound may have been caused accidentally (*e.g.*, abrasion, cut, broken bone), intentionally (*e.g.*, surgical wound), or by a disease process (*e.g.*, infarction). The factors produced by the inventive method are not limited to angiogenic factors but may include other factors that might contribute to wound healing (*e.g.*, cytokines, prostaglandins, leukotrienes, growth factors, chemotaxis factors, *etc.*). These factors may be produced within the wounded tissue itself, or outside the wounded tissue and transported to the site of injury.

In another aspect, the present invention provides an apparatus for providing external compression so that angiogenesis is induced. The apparatus comprises a fluid or gas, a compression structure for receiving and compressing the fluid or gas, and a control means for

controlling the inflation and deflation of the compression structure. Optionally, the apparatus may contain other diagnostic and control features such as a blood oxygen detector, a pulse oximeter, EKG detector, a blood pressure detector, doppler flow probe, *etc.* In certain particularly preferred embodiments, the deflation and inflation of the compression structure is synchronized to the cardiac cycle. Preferably, the compression phase (*i.e.*, inflation of the compression structure) is anti-phase to left ventricle systole. In another particularly preferred embodiment, the gas or fluid is withdrawn from the compression means using a vacuum pump or a negative pressure reservoir.

Definitions

The term *animal*, as used herein, refers to humans as well as non-human animals, including, for example, mammals, birds, reptiles, amphibians, and fish. Preferably, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a primate, or a pig). An animal may be a transgenic animal.

The term *compression*, as used herein, refers to the application of pressure to an area of the body. Preferably, the compression is exerted externally. The compression may be applied to any part of the patient's body. In a particularly preferred embodiment, the pressure used to provide the compression is less than 300 mm Hg, more preferably less than 200 mm Hg, and most preferably less than 150 mm Hg.

The term *factor*, as used herein, refers to any molecule, peptide, protein, nucleic acid, or natural product that is produced or secreted by cells responding to the external compression. Examples of factors included, but are not limited to, mitogens, growth factors, platelet-derived growth factors A and B, basic fibroblast growth factor, epidermal growth factor, vascular

endothelial-derived growth factor, nitric oxide, endothelin-1, transforming growth factor• 1, prostaglandins, leukotrienes, and cytokines. In certain preferred embodiments, the factor is an angiogenic factor. In other preferred embodiments, the factor is known to promote wound healing.

The term *graded*, as used herein, refers to a form of compression wherein the pressure applied at a distal region is greater than the pressure applied at a more proximal region. For example, the pressure applied at the ankles is greater than the pressure applied at the calves. In a particularly preferred embodiment the difference between the distal and proximal ends of the compression region is between about 10 mm Hg and about 100 mm Hg, more preferably the difference is between about 30 mmHg and about 80 mm Hg, and most preferably the difference is between about 40 mm Hg and about 60 mm Hg.

The term *hemodynamic force*, as used herein, refers to any force related to or resulting from blood flow. Hemodynamic forces include, but are not limited to, fluid shear stress, solid stress, blood flow, and pressure. In a particularly preferred embodiment, the hemodynamic forces are experienced by the cells that subsequently produce the desired factors. In a particularly preferred embodiment, the hemodynamic force is shear stress.

The term *sequential*, as used herein, is synonymous with wave-like and refers to a form of compression wherein a wave of compression is generated. For example, compression is first applied distally and subsequently is applied further and further proximally. The compression wave may be retrograde or antegrade with respect to normal blood flow. Preferably, the compression wave is retrograde with respect to normal blood flow. In a preferred embodiment, the speed of the wave of compression resulting from sequential compression is comparable to the speed of propagation of pulse waves through the peripheral arteries. In another preferred

embodiment, the speed of the wave ranges from about 2 m/s to about 15 m/s, more preferably from about 5 m/s to about 10 m/s.

Brief Description of the Drawing

Figure 1 shows (a) the 30 element model of the arterial system. Dashed elements represent those that are reflected by symmetry and are not explicitly computed. b) Division of lower arterial tree elements into three pressurization regions for EECP model. The figure is drawn to scale.

Figure 2 depicts the application of external pressure with respect to time during the heart cycle. Parameter values are given in Table 3.

Figure 3 shows the pressure at several locations in the arterial tree with normal parameter values ("normal") and parameter values simulating compromised ventricular function ("diseased"). One complete cardiac cycle at steady state is shown, beginning with the onset of systole. Parameter values as given in Table 3. Greater augmentation, as evidenced by greater values of the effectiveness ratio, is seen in the simulated disease cases: (a) radial artery, normal. Method for computing "effectiveness ratio" shown; (b) aortic root, normal; (c) radial artery, diseased; and (d) radial, aortic, and abdominal pressures, diseased.

Figure 4 is a graph of cross-sectional area plotted versus time for several cardiac cycles following the onset of EECP at the midpoint of the (a) lower abdomen, (b) thigh, and (c) calf compression zones, respectively, normalized with respect to the cross-sectional area without external compression at 100 mm Hg (A_o). Light lines: no external compression. Dark lines: with external compression.

Figure 5 is a measure of arterial wall shear stress [Eq. (23)] plotted versus time for several cardiac cycles following the onset of EECP at the midpoint of the (a) lower abdomen, (b) thigh, and (c) calf compression zones, respectively. Magnitude is increased by more than 3-fold (much more in the lower abdomen) and flow reversal is evident. Light lines: no external compression. Dark lines: with external compression. Note that mean shear stress in the normal arterial circulation is generally in the range of 1.5 Pa.

Detailed Description of Certain Preferred Embodiments of the Invention

The present invention provides a system for inducing angiogenesis or wound healing by the use of external compression. Compression of a part of the patient's body is thought to lead to changes in hemodynamic forces experienced by cells of the vasculature which in turn respond to the change by producing and secreting various factors. These factors may act locally or distantly to induce angiogenesis or wound healing and thereby prevent or reduce the patient's disease.

Patients

The patient treated by the inventive external compression method of inducing angiogenesis may be any animal including humans suffering from any pathological or physiological state that would benefit from the growth of new blood vessels. In a particularly preferred embodiment, the patient being treated by the inventive method suffers from low blood flow and/or reduced perfusion of a limb, organ, tissue, or group of cells. Some disease states that are characterized by low blood flow include, but are not limited to, cardiovascular disease, coronary artery disease, peripheral vascular disease, peripheral vascular disease resulting from diabetes (Type I or Type II), peripheral atherosclerotic disease, atherosclerosis, thromboangiitis

obliterans, Raynaud's phenomenon, arteritis, vasculitis, thromboembolic disesase, intermittent ischemic pain, claudication, intermittent claudication, gangrene, vascular insufficiency, resting pain, microemboli, *etc.* The inventive method preferably helps to increase perfusion of the affected area by the formation of new blood vessels. In certain preferred embodiments, these newly created blood vessels are collateral blood vessels that by-pass an obstructed or partially obstructed vessel.

In another preferred embodiment, the patient has a wound or injury, and the inventive method of external compression is used to promote wound healing. The promotion of wound healing is preferably by the stimulation of growth of new blood vessels; however, the inventive method is not limited to inducing the growth of new blood vessels but could be due to the action of induced growth factors, mitogens, cytokines, and other regulatory molecules on the cells of the injured tissue. The wound may be any injured or damaged organ, tissue, cell, groups of cells, body part, or limb. The wound may have been created intentionally as in a surgical incision, or the wound may have occurred via a disease process such as a myocardial infarction due to coronary artery disease. The wound may also be a cut, scratch, abrasion, bruise, broken bone, *etc.*

The inventive method may also be applied to non-human animals. In a preferred embodiment, the inventive method is used to stimulate angiogenesis or promote wound healing in mammals. In a particularly preferred embodiment, the mammals are domesticated. As in the case of humans, animals being treated by the inventive method suffer from low blood flow to an affected area or have a wound or injured tissue.

Compression

A compression apparatus is attached to at least one body part of the patient being treated by the inventive method. Preferably, the apparatus is attached to the outside of the patient and thereby induces angiogenesis or wound healing in a non-invasive manner. The apparatus is preferably attached relatively close to the area of low blood flow so that any induced, short-lived factors produced by the compression are delivered to the affected area before significant degradation. The compression apparatus may be attached to the patient using any means known in the art. These may include Velcro® straps, zippers, elastic bands, buttons, snaps, *etc.*

The compression apparatus preferably compresses the blood vessels of the body part to which the apparatus is attached. This leads to a change in the environment (*e.g.*, hemodynamic forces, mechanical strain, blood flow, pressure, shear stress) of the cells of the vessels (*e.g.*, endothelial cells, fibroblasts, smooth muscle cells, *etc.*). Many of these cells are known to respond to changes in their environment. For example, endothelial cells are known to respond to changes in shear stress (Davies "Mechanisms involved in endothelial responses to hemodynamic forces" *Atherosclerosis* 131:S15-S17, June 1997; Diamond *et al.* "Tissue plasminogen activator messenger RNA levels increase in cultured human endothelial cells exposed to laminar shear stress" *Journal of Cell Physiology* 143:364-371, 1990; Hseih *et al.* "Shear stress increases endothelial platelet-derived growth factor mRNA levels" *American Journal of Physiology* 260:H642-H646, 1991; Malek *et al.* "Fluid shear stress differentially modulates expression of genes encoding basic fibroblast growth factor and platelet-derived growth factor B chain in vascular endothelium" *Journal of Clinical Investigation* 92:2013-2021, 1993; Mason "The ins and outs of fibroblast growth factors" *Cell* 78(4):547-552, August 1994; Mitsumata *et al.* "Fluid shear stress stimulates platelet-derived growth factor expression in endothelial cells" *American Journal of Physiology* 265(1):H3-H8, July 1993; Sumpio "Hemodynamic forces and the biology

of the endothelium: signal transduction pathways in endothelial cells subjected to physical forces in vitro" *Journal of Vascular Surgery* 13(5):744-746, May 1991; Ichioka *et al.* "Effects of shear stress on wound-healing angiogenesis in the rabbit ear chamber" *Journal of Surgical Research* 72:29-35, 1997; each of which is incorporated herein by reference). In response to the change, the cells produce a variety of factors including platelet-derived growth factors A and B and basic fibroblast growth factor.

Any pattern of pressure application may be used in the inventive method. Preferably, the pressure application results in a change in a hemodynamic force experienced by the cells of the blood vessels being compressed as well as those up- and downstream of the compression site. In a particularly preferred embodiment, the endothelial cells are stimulated by a change in shear stress. Preferably, the change in shear stress results in a change in the sign of the shear stress indicating a change in the direction of blood flow. In other preferred embodiments, at least a 25% change in shear stress is observed, more preferably at least a 50% change, and most preferably at least a 100% change.

In certain preferred embodiments, the maximum pressure applied by the compression apparatus is greater than peak systolic pressure. In other preferred embodiments, the maximum pressure applied is less than 300 mm Hg, more preferably less than 200 mm Hg, and most preferably less than 150 mm Hg.

In certain preferred embodiments, graded pressure application is used in the inventive method. Graded refers to the application of more pressure distally than that applied proximally. In certain particularly preferred embodiments, the pressure difference between the distal and proximal ends of the compression region is in the range from about 20 mm Hg to about 100 mm

Hg, more preferably from about 30 mm Hg to about 70 mm Hg, and most preferably from about 40 mmHg to about 60 mm Hg.

In other preferred embodiments, the pressure application is wave-like or sequential. Sequential compression is produced by applying pressure distally first and proximally later, thereby generating a wave of compression that propagates toward the heart and is retrograde with respect to normal arterial blood flow in the patient. The speed of the compression wave is preferably comparable to the speed of wave propagation through the peripheral arteries. Preferably, the speed of the wave is from about 1 m/s to about 15 m/s, more preferably from about 5 m/s to about 10 m/s.

In yet other preferred embodiments, the pressure application is both graded and sequential.

In certain preferred embodiments, the pressure exerted by the apparatus increases and decreases as rapidly as possible to allow for the greatest degree of emptying and filling of the compressed vessels. Preferably, the inflation and deflation periods are from about one-hundredth of a second to about one second, more preferably from about 0 sec to about 0.5 second.

In certain preferred embodiments the external compression of the body part(s) is optimized for the purpose of maximizing the stimulus to the arterial endothelium of the peripheral arteries and thereby induce the secretion of angiogenic factors. Others have attempted to optimize external compression based on the notion that this can produce a reduction in systolic afterload or diastolic augmentation. If one wishes to treat a patient with coronary artery disease through angiogenesis, the external compression applied would preferably be optimized to lead to a change in shear stress in the arteries of the coronary circulation, aortic root, or the lower extremities. Such parameters that need to be considered in optimizing the external compression

for the stimulation of angiogenic factors include, but are not limited to, maximum pressure, timing, method of applying pressure (*e.g.*, graded, sequential, *etc.*)

In other preferred embodiments, the external compression is optimized to stimulate the largest area of endothelial cells. For example, compressions may not only stimulate the vessels actually being compressed but may also affect those upstream such as the aorta and those downstream such as the arterioles and capillary bed.

In certain particularly preferred embodiments, the pattern of pressure application is timed with the cardiac cycle. Preferably, pressure application is antiphase to left ventricle systole (*i.e.*, external pressure is applied during diastole). Timing the pressure application with the heart in this manner does not lead to stress on the heart and may lead to augmentation of blood flow and a reduction in cardiac afterload. In one particularly preferred embodiment, compression and decompression is synchronized with the patient's electrocardiogram (ECG). For example, the compression period may begin at the end of the T-wave of the EKG signal and may end at the R-wave. For a more detailed discussion of inflating and deflating a balloon based on an ECG signal, please see U.S. patents 3,707,960 and 4,692,148, each of which is incorporated herein by reference.

The external compression leads to a change in the environment of the cells in the blood vessels due to the effect of the compression on various hemodynamic forces. Cells that may be affected by the compression include, but are not limited to, endothelial cells, fibroblasts, muscle cells, smooth muscle cells, blood cells (*e.g.*, leukocytes, platelets), and epithelial cells. The cells respond to the change in their environment by producing various factors including angiogenesis factors, platelet-derived growth factor, fibroblast-derived growth factor, epidermal growth factor, vascular endothelial-derived growth factor, mitogens, prostaglandins, nitric oxide (NO),

leukotrienes, and cytokines. Some of these factors such as NO may only act locally where they are produced due to their short half-lives. Others such as the growth factors may be transported in the blood to other locations and affect distant cells. The affected cells will preferably have receptors for the growth factor. In a particularly preferred embodiment, the cells of the affected area with reduced blood flow or suffering from injury will have receptors for these factors made elsewhere in the body and induced by external compression.

The external compression method may be applied to a patient periodically, continuously, or only once. Preferably, the method is applied to a patient numerous times at set intervals until blood flow is restored, wound healing occurs, or symptoms are decreased. For example, external compression may be applied to a patient suffering from peripheral vascular disease 1-5 times a day for one half hour each time over 3-6 weeks in order to promote the growth of new blood vessels in the low extremities. The inventive method may also be used prophylactically. For example, a diabetic patient at risk for peripheral vascular disease may be treated with external compression to reduce the chances of later developing peripheral vascular disease and the complications thereof. The regimen to be followed may be determined by one of skill in the art by taking into consideration such factors as the desired endpoint, the severity of the reduced blood flow or wound, the patient's initial response to the treatment, the patient's wishes, the patient's overall condition, *etc.* As with any medical treatment, it would be appreciated by one of skill in this art that a patient's treatment regimen should preferably be tailored to each individual treated.

In another particularly preferred embodiment of the present invention, in addition to or instead of a positive pressure being applied to a body part, a negative pressure with respect to atmospheric pressure is used in the inventive method. The apparatus for delivering the negative

pressure would house a part of a patient's body substantially sealed off from the atmosphere so that a negative pressure reservoir such as a vacuum pump could be used to reduce the pressure inside the apparatus for a period of time. The apparatus may then be pressurized back up to atmospheric pressure or above atmospheric pressure. The pressurization/depressurization cycles may be timed to the cardiac cycle of the patient in much the same way as the compression method may be synchronized with the patient's cardiac rhythm. Negative pressure may be used, for example, to enhance refilling of collapsed arteries.

Apparatus

The present invention also provides an apparatus for carrying out the inventive method of external compression for inducing angiogenesis or wound healing. The apparatus comprises a source of liquid or gas, a compression structure for receiving the liquid or gas, and a control means for achieving inflation and deflation of the compression structure. The control means controls the flow of the gas or liquid into and/or out of the compression structure, thereby applying pressure to the body part to which the compression structure is attached.

The liquid or gas used to inflate the compression structure of inventive apparatus may be any gas or liquid. Preferred gases include, but are not limited to, air, nitrogen, argon, helium, carbon dioxide, and mixtures thereof. Preferred liquids include, but are not limited to, water, a buffered aqueous solution, a polymer solution, and an organic liquid.

The compression structure is a balloon or bladder capable of receiving the gas or liquid and exerting a pressure on the body part to which the compression structure is attached. In a particularly preferred embodiment, the compression structure is made of a polymer or plastic material. In a particularly preferred embodiment, the compression structure is capable of being

distended without tearing or rupture. The compression structure is attached to the body part of the patient by Velcro® straps, zippers, elastic bands, buttons, snaps, *etc.* It will be appreciated by one of skill in this art that the dimensions and shape of the compression apparatus will depend on the patient to which it is being attached as well as on the body part to which the compression apparatus is being attached.

The compression structure may also be a band with variable tension. These bands may be wrapped around an extremity or around a patient's midsection. The tension in the bands may then be adjusted to provided the required external compression. The length and width of the band, as would be appreciated by one of skill in this art, will depend on the patient's size, the extremity to which it is applied, the amount of tension to be applied, *etc.* The bands may be continuous or the ends may be attached together using snaps, an adjustable fastener, buttons, Velcro®, zippers, *etc.* For an example of such a compression structure, please see U.S. Patent 5,407,418, issued April 18, 1995; incorporated herein by reference.

The control means controls the inflation of the compression structure by allowing the fluid or gas to flow into the compression structure. For example, in the case of a pressurized gas the control means may open a valve which allows the pressurized gas to flow into the compression structure. In another example, the control means may turn on a pump that delivers a gas or a liquid into the compression structure.

The apparatus may also comprise a means for accelerating the withdrawal of the liquid or gas from the compression structure (*e.g.*, vacuum pump or a negative pressure reservoir). In a preferred embodiment, the control means controls the withdrawal means and thereby controls deflation of the compression structure. For example, the control means may open a valve

connecting the vacuum pump with the compression structure to allow for the quick evacuation of the gas or liquid.

The apparatus may optionally comprise a blood oxygen detector, a pulse oximeter, an EKG detector, a blood pressure monitor, a heater, and/or a refrigeration unit The additional devices may be used to monitor the status of the patient, or they may be used to time the inflation and deflation of the compression structure. In a particularly preferred embodiment, the pulse oximeter, EKG detector, or blood pressure monitor is interfaced with the control means so that the control means can time the inflation and deflation of the compression structure to certain events in the cardiac cycle. For example, at the end of systole, the compression means inflates, and before systole begins, the compression means deflates.

In another preferred embodiment, instead of the compression structure being an inflatable bladder, the apparatus uses flexible bands, and the tension in the bands is used to apply external compression to the body part. The tension in the band is controlled by the control means and may be timed with the cardiac cycle as described above.

These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

Examples

Example 1-Numerical Simulation of Enhanced External Counterpulsation

Introduction

Enhanced external counterpulsation (EECP) is a non-invasive, counterpulsative procedure providing temporary support for the failing heart. EECP involves surrounding the lower half of a patient's body (lower abdomen, thighs, and calves) with inflatable cuffs that are pressurized and depressurized approximately out-of-phase with the left ventricle. While the aortic valve is closed (ventricular diastole), pressurization of the cuffs collapses the arteries causing the blood stored in the lower extremities to be directed retrograde toward the heart. The resultant increase in aortic diastolic pressure has the potential to increase blood flow to vital organs, especially the heart, which receives much of its perfusion during diastole. Just prior to ventricular ejection (systole), the cuffs are depressurized to atmospheric pressure and the collapsed arteries begin to refill. This causes a rarefaction wave to propagate retrograde reaching the heart during cardiac systole, thereby decreasing cardiac afterload.

EECP has been tested as a means of cardiac assist in patients suffering from cardiogenic shock (Sorroff, H.S., Cloutier, C.T., Birtwell, W.C., Begley, L.A., Messer, J.V. External counterpulsation, management of cardiogenic shock after myocardial infarction. *J. Am. Med. Assn.* 229:14411450, 1974; incorporated herein by reference) and acute myocardial infarction (Parmley, W.W., Chatterjee, K., Charuzi, Y., Swan, H.U. Hemodynamic effects of noninvasive systolic unloading (nitroprusside) and diastolic augmentation (external counterpulsation) in patients with acute myocardial infarction. *Am. J. Cardiol.* 33:819-825, 1974; incorporated herein by reference), and as treatment for cardiac ischemia and angina (Lawson, W.E., Hui, J.C., Zheng, Z.S., Burgen, L., Jiang, L., Lillis, O., Oster, Z., Soroff, H., Cohn, P. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? *Cardiology,.* 87(4):271-275, 1996; Lawson, W.E., Hui, J.C., Soroff H.S., Zheng, Z., *et al.* Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *American Journal of*

Cardiology, 70(9):859-862, 1992; each of which is incorporated herein by reference). Despite some success in these trials EECP is not currently used as a means of cardiac assist. It is, however, gaining acceptance as a treatment for patients suffering from cardiac ischemia and severe angina secondary to coronary disease (Amsterdam, E.A., Banas, J., Cartley, J.M., *et al.* Clinical assessment of external pressure circulatory assistance in acute myocardial infarction. *Am. J. Cardiol.*, 45:349, 1990; Lawson, W.E., Hui, J.C., Soroff H.S., Zheng, Z., et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *American Journal of Cardiology*, 70(9):859-862, 1992; Zheng, Z.S., Li, T.M., Kambic H., *et al.* Sequential external counterpulsation (SECP) in China. *Transactions of the American Society of Artificial Internal Organs*, 29:599-603, 1983; each of which is incorporated herein by reference) based on strongly favorable results from a recent multi-center study (Arora, R.R., Chou, T.M., Jain, D., Fleishman, B., Crawford, L., McKiernan, T., Nesto, R.W. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J. Am. Col. Cardiol.*, 33(7):1833-1840, 1999; each of which is incorporated herein by reference).

Despite this success, the mechanisms by which EECP reduces angina and improves cardiac function remains unclear. It has been proposed that factors other than the purely mechanical ones may be responsible, and that EECP may enhance the development of collateral vessels in the coronary circulation. For example, Soran *et al.* recently argued that the beneficial effects of EECP might be a consequence of angiogenic factors released as a result of increased shear stress (Soran, A.U., Crawford, L.E., Schneider, V.M., and Feldman, A.M. Enhanced external counterpulsation in the management of patients with cardiovascular disease. *Clinical Cardiology*, 22(3): 173-178, 1999; incorporated herein by reference).

Here we extend that thesis, and propose that the vascular (endothelial and/or smooth muscle) cells of the lower extremity may be a source of these factors since the enhancement in shear stress is far more dramatic there than elsewhere in the circulation, and the endothelial surface area quite large. We therefore consider not only on the changes in aortic root pressure as it relates to direct, mechanical cardiac effects and coronary blood flow, but also arterial collapse and the augmentation of hemodynamic shear stress that accompany lower extremity compression. A new cardiovascular fluid mechanics model is presented that allows us to simulate the hemodynamics associated with EECP to determine how the operating parameters of the device influence its performance.

Methods

The Cardiovascular Model

Governing equations. Following Stettler *et al.* (Stettler, J.C., Niederer, P. and Anliker, M. Theoretical analysis of arterial hemodynamics including the influence of bifurcations. Part I: Mathematical Model and Prediction of Normal Pulse Patterns. *Annals of Biomedical Engineering* 9:145-164, 1981; incorporated herein by reference), we consider the one-dimensional form of the equations of motion since we are interested in the mean values of pressure and flow at specific locations in the arteries. Furthermore, higher dimensional flow problems are at present too computationally expensive to be of practical use. One-dimensional flow in an elastic artery can be described using the basic equations for momentum and continuity:

$$\frac{\partial}{\partial t}[\mathbf{A}]+\frac{\partial}{\partial x}[\mathbf{B}]+[\mathbf{C}]=0 \qquad (1)$$

where

$$[\mathbf{A}]=\begin{bmatrix} u \\ A \end{bmatrix},\quad [\mathbf{B}]=\begin{bmatrix} u^2/2+P/\rho \\ uA \end{bmatrix},\ \text{and}\quad [\mathbf{C}]=\begin{bmatrix} F \\ \Psi \end{bmatrix} \qquad (2), (3), (4)$$

where u and P are the local cross-sectional average velocity and pressure, A is the cross-sectional area, and F is the frictional loss, to be described later in further detail. The term Ψ representing minor branch flow in the continuity expression represents the distributed outflow per unit length and is approximated as a linearly resistive element, described by the equation

$$\Psi(P,x)=\Phi(x)(P-P_v) \qquad (5)$$

Here the driving force for flow is the pressure drop between the local arterial pressure and the uniform venous pressure P_V. The constant $\Phi(x)$ describes the spatial distribution of flow into smaller branches.

A pressure-area relation or "tube law" may be formulated to provide a third independent equation. This relationship will be described below. The set of hyperbolic, partial differential equations in Eq. (1) for the arterial elements are solved using an adaptation of the MacCormack two step predictor-corrector method (Anderson, D.A., Tannenhill, J.C., and Pletcher, R.H. *Computational Fluid Mechanics and Heat Transfer*. McGraw Hill, New York, 1984; incorporated herein by reference).

The expression for the frictional loss F in Eq. (4) may be derived as follows. The general form of the frictional or viscous loss term is given by the expression:

$$F=-\frac{2\tau_o}{\rho R} \qquad (6)$$

where R is the arterial radius. From Young and Tsai (Young, D.F., Tsai, F.Y. Flow

characteristics in models of arterial stenoses- II. Unsteady flow. *J. Biomechanics* 6: 547-559, 1973; incorporated herein by reference) the shear stress term may be represented as:

$$\tau_o = \frac{4C_v\mu}{R}\cdot u(t) + \frac{\rho}{2\pi R}\cdot(C_u - 1)\cdot\frac{\partial Q}{\partial t} \qquad (7)$$

where C_u and C_v are functions of the local frequency parameter α:

$$\alpha = R_o \cdot \sqrt{\frac{\omega}{\nu}} \qquad (8)$$

Here R_o is the arterial radius, ω is the angular frequency of oscillation, and ν is the kinematic viscosity of the fluid. Young and Tsai (Young, D.F., Tsai, F.Y. Flow characteristics in models of arterial stenoses- II. Unsteady flow. *J. Biomechanics* 6: 547-559, 1973; incorporated herein by reference) give plots of C_u and C_v versus α, from which algebraic approximations were generated for use in the model.

A hybrid tube law was used to describe the relationship between arterial cross-sectional area and transmural pressure. During arterial collapse, the steady state shear term in Eq. (7) is increased by a factor of three to reflect the change in cross-sectional shape (Kamm, R.D., and Shapiro, A.H. Unsteady flow in a collapsible tube subjected to external pressure or body forces. *J. Fluid Mech.* 95:1-78, 1979; incorporated herein by reference). We also modify the tube law used by Stettler *et al.* (Stettler, J.C., Niederer, P. and Anliker, M. Theoretical analysis of arterial hemodynamics including the influence of bifurcations. Part I: Mathematical Model and Prediction of Normal Pulse Patterns. *Annals of Biomedical Engineering* 9:145-164, 1981; incorporated herein by reference) to avoid a singularity that arises at negative transmural pressures. The modified forms are used when $A/A_0 < 0.36$ where A_o is the area at a reference

pressure $P_o = 100$ mmHg (13.3 kPa) and has the form:

$$P_{tm} = P_{tm}(A) + \eta \frac{\partial A}{\partial t} \tag{9}$$

Here the transmural pressure P_{tm} is the difference between the internal and external pressures across the artery wall and is related to the cross-sectional area through the expressions given in Table 1. The term $P_{tm}(A)$ in Eq. (9) represents the elastic response associated with a static transmural pressure, and η is a damping coefficient. A value of $2.0\text{x}10^5$ N s m^{-4} was used for η in the model, selected based on comparisons to a previous, somewhat more rigorous model for viscoelasticity (Holenstein, R., Niederer, P., Anliker, M. A viscoelastic model for use in predicting arterial pulse waves. *J. Biomech. Eng.*, 102:318-324, 1980; incorporated herein by reference) as described in Bottom (Bottom, K.E. "A numerical model of cardiovascular fluid mechanics during exernal cardiac assist." Thesis, S.M., Massachusetts Institute of Technology, May, 1999; incorporated herein by reference). The actual form of the tube law expressing area as a function of pressure is solved using a binomial expansion approximation applied to Eq. (9). The equations required for calculation of the hybrid tube law are summarized in Table 1 for both the collapsed and uncollapsed regimes.

Table 1. Forms used to describe the elastic response of the artery in the numerical solution. Different forms were required to capture the behavior of the distended (A• A_T) and collapsed ($A<A_T$) vessels.

Inverse tube law	A• A_T	$P_{tm} = \left[\dfrac{P_0 + \rho c_0 g(z) \chi_0 \ln\left(\dfrac{A}{A_0}\right)}{1 - \rho c_0 B g(z) \ln\left(\dfrac{A}{A_0}\right)} \right] + \eta \dfrac{\partial A}{\partial t}$
	$A<A_T$	$P_{tm} = P_0 + \rho c_0 g(z)(\chi_0 + BP_T)\ln\left(\dfrac{A}{A_0}\right) + \eta \dfrac{\partial A}{\partial t}$
Elastic response	A• A_T	$A^s = A_0 \exp\left[\dfrac{P_{tm} - P_0}{\rho c_0 c(P,z)}\right]$
	$A<A_T$	$A^s = A_0 \exp\left[\dfrac{P_{tm} - P_0}{\rho c_0 g(z)(\chi_0 + BP_T)}\right]$
Wave speed	A• A_T	$c(P,z) = g(z)(\chi_0 + BP_{tm})$
	$A<A_T$	$c(P,z) = \sqrt{g(z)c_0(\chi_0 + BP_T)}$

Notes:

• Condition for collapse is $A < A_T$, where A is the cross-sectional area, and A_T is the transitional area , $A_T = 0.36A_0$.

• P_{tm} is the transmural pressure.

• P_o is the reference pressure, equal to 100 mmHg (13.3 kPa).

• A_o is the elastic response at the reference pressure P_o.

• The constants B, χ_o, and the function $g(z)$ are obtained from experimental measurements as described in Stettler *et al.* (Stettler, J.C., Niederer, P. and Anliker, M. Theoretical analysis of arterial hemodynamics including the influence of bifurcations. Part I: Mathematical Model and Prediction of Normal Pulse Patterns. *Annals of Biomedical Engineering* 9: 145-164, 1981; incorporated herein by reference).

<u>Bifurcations</u>. The individual arterial segments are coupled through appropriate boundary

conditions. At bifurcations where a single tube branching into separate daughter tubes we write the equation of energy conservation for a control volume corresponding to a stream tube that includes all of the flow entering the *n*th daughter branch (Wolf, T. "An Experimental/Theoretical Investigation of Parallel Inhomogeneities in Respiratory Flows." Ph.D. thesis, Dept. of Mechanical Engineering, Massachusetts Institute of Technology: June, 1990; incorporated herein by reference):

$$\begin{aligned}\rho\frac{\partial u_1}{\partial t}x_1+\rho\frac{\partial u_n}{\partial t}x_n+P_n+\frac{1}{2}\rho\left(u_n^2 f_n+u_n|u_n|k_n\right)-P_1-\frac{1}{2}\rho u_1^2\\+\frac{1}{2}\rho u_n|u_1u_n|^{1/2}\lambda_n=0\end{aligned}\qquad(10)$$

where the subscript "1" denotes the parent branch and the subscript "*n*", one of the daughter branches. The absolute values of velocity are incorporated to preserve the directionality of the losses as the flow changes direction. The unsteady continuity equation for the control volume encompassing the entire bifurcation including all daughter vessels is written as:

$$\frac{\partial A_1}{\partial t}x_1+\frac{\partial A_2}{\partial t}x_2+\ldots+\frac{\partial A_N}{\partial t}x_N-u_1A_1+u_2A_2+..+u_NA_N=0\qquad(11)$$

where *N* is the total number of elements connected at a bifurcation, including the parent branch. The equations of motion are coupled with momentum, continuity and the hybrid tube law are applied at the interface between an element and the bifurcation control volume.

The term f_n in Eq. (10) representing the ratio of actual kinetic energy flux at *n* to that corresponding to a flat velocity profile is assumed to approach unity in the parent branch. The coefficients λ_n and k_n are dimensionless head loss coefficients due to "entrance type" and "turbulent type" losses, respectively. Following Pedley *et al.* (Pedley, T.J., Schroter, R.C. and Sudlow, M.F. Energy losses and pressure drop in models of human airways. *Resp. Physiol.*